REMARKS

Claims 1-3 and 5-9 are currently pending in the application.

Claims 4 and 10 have been cancelled without prejudice or disclaimer, solely to expedite patent prosecution in accordance with the U.S. Patent Office Business Goals (65 Fed. Reg. 54604 (September 8, 2000)). Applicant reserves the right to present the cancelled claims in a co-pending application.

Claims 11 and 12 have been withdrawn by the Examiner as being directed to non-elected subject matter.

Claims 1-3 and 5-9 have been amended for clarity, to reduce duplication, and to more fully encompass Applicant's invention. Applicant reserves the right to present any cancelled subject matter in a co-pending application.

Claim 1 has been amended to recite "...establishing a proteomic map comprising: (a) determining proteomic interactions of a protein in the absence of a simulated redox state perturbation ; (b) determining proteomic interactions of a protein in the presence of a simulated redox state perturbation; and (c) generating the proteomic map by identifying the different proteomic interactions between (a) and (b)." (See, *inter alia*, page 3, lines 12-19; page 6, line 14 to page 7, line 5; page 8, lines 10-22; page 11, lines 13-19; and Example I, page 22, lines 5-8 of the originally filed application).

Claim 2 has been amended to recite various processes for generating the redox state perturbation. (See, *inter alia*, page 11, lines 14-18 and page 12, lines 20-21 of the originally filed application).

Claim 3 has been amended to recite use of various redox state modifier molecules to generate the redox state perturbation. (See, *inter alia*, page 12, lines 9-19 of the originally filed application).

Claim 5 has been amended to recite "...correlating proteomic-interaction(s) with oxygen tension comprising (a) determining proteomic interactions of a protein in room air; (b) determining proteomic interactions of a protein in the presence of decreased oxygen tension; and (c) correlating the proteomic interaction(s) with oxygen tension by identifying different proteomic interactions between (a) and (b)." (See, *inter alia*, page 5, lines 6-9; page 19, lines 1-4; and Example I, page 22, lines 5-8 of the originally filed application).

Claim 6 has been amended to correct typographical error, by substituting "is" for "are."

Claim 7 has been amended to refer to step (b) in Claim 5.

Claim 8 has been amended to recite the range of decreased oxygen concentration in step (b) of Claim 5 to be from 0.1 mm Hg to 145 mm Hg. (See, *inter alia*, page 19, lines 19-20 of the originally filed application).

Claim 9 has been amended to clarify how the output of step (c) can be used to identify protein functions associated with a pathophysiological process. (See, *inter alia*, Examples I-II and IV of the originally filed application).

These amendments are supported by the application as originally filed, and do not constitute new matter. Specific support for the amendments is shown in parentheses, above. Entry of these amendments in the application is respectfully requested.

Election/Restriction

In the Office Action, the Examiner has stated that the restriction requirement has been deemed final and Claims 11 and 12 have been withdrawn from consideration (Office Action, page 3). This is reflected in the listing of the claims shown above.

Rejection under 35 U.S.C. §112, First Paragraph

Claims 1-10 have been rejected under 35 U.S.C. § 112, first paragraph. The Examiner contends that the claims are not enabled because "[w]ithout a clear indication of what diseases can be examined under altered redox conditions, the skilled artisan would be unable to use the claimed invention because the skilled artisan would not know for which disease they were establishing a protein interaction map." (Office Action, page 5). Applicant respectfully traverses.

Applicant has amended the claims to clarify that the currently claimed invention. As amended, the claims recite methods for generating a proteomic interaction map by comparing proteomic interactions in the absence of a simulated redox state perturbation with proteomic interactions in the presence of a simulated redox state perturbation. The claims are fully enabled, as detailed below.

First, methods for generating proteomic interactions (e.g., protein-protein interactions) are well known in the art, and the specification as filed provides sufficient guidance to the ordinarily skilled artisan to carry out the claimed methods.

The application specifically teaches that protein-protein interactions and protein activities and levels can be measured by well-known means, including two-hybrid analysis, protein chips (Fung et al., 2001), subtractive antibody screening (Hare et al., 1998), microarrays (Ren et al., 2000) (see, *inter alia*, page 9, line 3 to page 11, line 8). Two-hybrid protein-protein interaction systems are expressly recited and US patent Nos. 6,083,693 and 6,187,535 are expressly recited (see, *inter alia*, page 9, lines 13-16). These patents are presumed valid and enabled. Thus, the ordinarily skilled artisan could carry out these disclosed methods to determine the proteomic interactions of a protein in the absence of a simulated redox state perturbation or in room air, as set forth in step (a) of amended Claims 1 and 5 and the corresponding dependent claims.

In addition, the instant application teaches that proteomic interactions can be screened in normal redox conditions (e.g., room air) and altered redox conditions (e.g., reduced oxygen tension), and the interactions identified from these screens can be compared (see, *inter alia*, working Examples I and Examples II-IV). Thus, with the instant specification in hand, the ordinarily skilled artisan could further repeat that process in the presence of a redox state perturbation as required by step (b) of amended Claims 1 and 5 and the corresponding dependent claims. In addition, the artisan could compare the results of the two steps as called for in step (c) of amended Claims 1 and 5 and the corresponding dependent claims. No undue experimentation is required.

The Examiner asserts that the scope of the claims is very broad since there are a multitude of pathological conditions that have nothing to do with altered redox states (Office Action, page 5). As amended, the claims of the instant application are not directed to such pathological conditions. The Examiner further asserts that the claimed methods involve a great deal of unpredictability, since they require the establishment of a causal relationship between protein interactions and disease states (Office Action, page 6). However, as currently written, amended Claims 1 and 5 have no requirement for such a causal relationship. These grounds for rejection are moot.

Second, the instant application provides ample guidance on how to accomplish the redox state perturbation called for in step (b) of amended Claims 1 and 5.

The application teaches that the simulated redox state perturbation may be generated by a process

selected from the group consisting of variation of concentration of redox state modifier molecules from physiological state, variation of glucose concentration from physiological state, presence of metal ions, alteration in NADH ratio, and oxygen concentrations less than room air (see, *inter alia*, page 11, line 13 to page 13, line 20, working Example I, and Examples II-IV).

In addition, the instant specification recites specific redox state modifier molecules that may be used to accomplish the redox state perturbation. The specification teaches that the simulated redox state perturbation may be generated by addition of a redox state modifier molecule such as superoxide, peroxides, hydrogen peroxide, alkoxides, sulfoxides, brominating species, chlorinating species, nitrosating molecules, nitric oxide, S-nitrosothiols, nitrating molecules, peroxynitrite, NO^- generating molecules, glutathione-regulating enzymes, NADH-regulating enzymes, and flavin-regulating enzymes (see, *inter alia*, page 11, line 13 to page 13, line 20, working Example I, and Examples II-IV).

The instant application demonstrates that proteomic interactions can be detected in room air and reduced oxygen tension (see, *inter alia*, working Example I, as well as Examples II and IV). The application teaches that altered redox conditions using different oxygen tensions can be employed, for example, in 5 or 10 mm Hg increments, and over the range from 0.1 mm Hg to 145 mm Hg (see, *inter alia*, page 19, lines 19-20 and page 20, lines 1-3).

The instant application further teaches that comparisons of interactions in normal and altered redox conditions can be used to generate a map that shows differences observed between the two conditions (see, *inter alia*, page 3, line 12 to page 4, line 14). In addition, the application teaches that specific alterations in redox conditions are well established as associated with various pathophysiological conditions, such as inflammatory bowel disease, p53-dependent cancers, diabetes, and Parkinson's disease (see, *inter alia*, page 12, line 1 to page 13, line 20).

Third, the Examiner states that the two-hybrid system has many shortcomings, including false positive results (Office Action, page 7). However, this is not relevant to the claims as amended.

Applicant's claims are directed to generating an improved proteomic interaction map. The claimed method compares proteomic interactions in the absence of a simulated redox perturbation (as is conventional) with proteomic interactions in the presence of simulated redox perturbation (which more closely simulates *in vivo* conditions). It does not matter to the claimed invention that the conventional yeast two-hybrid system may have shortcomings and may produce false positive results. The ordinarily

skilled artisan could nonetheless practice the claimed invention without undue experimentation since these disclosed methods for determining proteomic interactions are well-known and commonly used.

Applicant notes that the two-hybrid system of analysis is widely accepted in the art as a valid and verifiable approach for identifying interactions in the cell. Thus, two-hybrid systems are universally used and generally available from both academic and commercial sources including, for example, Invitrogen Corp. (Carlsbad, CA), BD Biosciences Clontech (Palo Alto, CA), Stratagene (La Jolla, CA), Paragon BioServices Inc. (Baltimore, MD), OriGene Technologies, Inc. (Rockville, MD), Qbiogene, Inc. (Carlsbad, CA), Applied Biosystems (Foster City, CA), Dualsystems Biotech AG (Zürich, Switzerland), Bio/Can Scientific, Inc. (Ontario, Canada), and MoBiTec GmbH (Göttingen, Germany), to name a few. Such widespread acceptance and use by skilled artisans is powerful evidence of the soundness of two-hybrid systems. The claimed method simply provides an improvement to the existing systems for analyzing proteomic interactions.

And, in any event, it is believed that Applicant's methods are less susceptible to error due to false positive results when employed with two-hybrid systems. This is because the claimed methods involve comparison of proteomic interactions in normal and altered redox conditions to determine the *differences* in interactions. Thus, false positives that arise under both normal and altered conditions would be "cancelled out" by Applicant's methods. Again, however, this is not relevant to consideration of whether the claimed method is enabled – it is – it merely demonstrates the superiority of the claimed method.

In addition, Applicant notes that the claimed methods are not required to perfectly identify each and every proteomic interaction under the appropriate standard for 35 U.S.C. § 112, first paragraph. It is well established that enablement is not precluded by the necessity for some experimentation, such as routine screening; the key is whether this experimentation is undue. *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Thus, Applicant concludes that in view of the detailed description, working example, and well-known techniques and factors disclosed in the instant application, it is respectfully asserted that the application provides sufficient guidance for the claimed methods. Reconsideration of pending Claims 1-3 and 5-9 is respectfully requested.

Rejection under 35 U.S.C. §112, Second Paragraph

Claims 3-10 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. In particular, the Examiner asserts that:

- Claim 3 lacks a process step recapitulating the preamble of the claim;
- Claim 3 lacks clarity as to what the method steps entail or to what they are directed;
- Claim 5 lacks a process step recapitulating the preamble of the claim; and
- Claim 9 lacks clarity as to how normal protein function can be determined in conditions of altered oxygen tension (Office Action, pages 11-13).

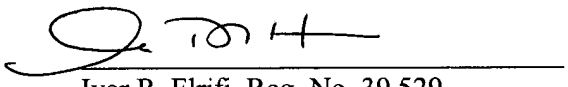
In this Amendment, Claim 3 has been amended to depend on Claim 1. Claim 5 has been amended for clarity and to more fully encompass Applicant's invention (see above). Claim 5 and Claim 9 have been amended to provide further clarity (see above). It is believed that the claim amendments obviate this ground of rejection. Reconsideration of pending Claims 1-3 and 5-9 is respectfully requested.

CONCLUSION

Applicant believes that the claims as amended are patentable and a prompt allowance is respectfully requested. If further discussion of this case is deemed helpful, the Examiner is encouraged to contact the undersigned at the telephone number provided below, and is assured of full cooperation in progressing the instant claims to allowance. Applicant believes no further fee is due at this time; however, the Commissioner is authorized to charge any additional fees that may be due, or to credit any overpayment, to the undersigned's account, Deposit Account No. 50-0311, Reference Number: 24862-503 (Customer Number: 35437).

Date: April 19, 2004

Respectfully submitted,



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